Sustained r l as lithium-containing tabl ts and m thod for their manufactur .

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Abstract

The release pattern of sustained release lithium carbonate tablets is improved by using a particular form of lithium carbonate material. This should have acicular crystals with a substantially monomodal particle size distribution in which the curve showing volume percentages of particles of different sizes shows a peak at a particle diameter of between 10 and 25 mu m. Moreover not more than 20% by volume of the material should have a particular diameter above 30 mu m. A preferred sustained release agent is a mixture of glyceryl mono-di- and tri-esters of straight chain saturated fatty acids. The tablets may be made by a moist granulation technique, followed by screening to ensure a granulate of appropriate grain sizes, after which the granulate is compacted into tablets.

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(54) **Sustained release lithium-containing tablets and method for their manufacture.**

(57) The release pattern of sustained release lithium carbonate tablets is improved by using a particular form of lithium carbonate material. This should have acicular crystals with a substantially monomodal particle size distribution in which the curve showing volume percentages of particles of different sizes shows a peak at a particle diameter of between 10 and 25 μm. Moreover not more than 20% by volume of the material should have a particular diameter above 30 μm. A preferred sustained release agent is a mixture of glyceryl mono-di- and tri-esters of straight chain saturated fatty acids.

The tablets may be made by a moist granulation technique, followed by screening to ensure a granulate of appropriate grain sizes, after which the granulate is compacted into tablets.

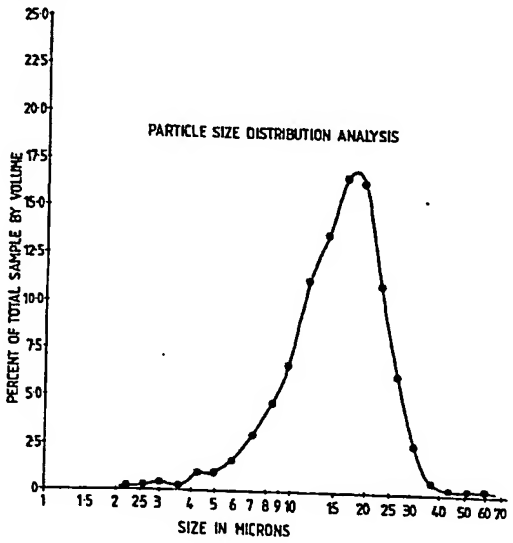

Fig.4

EP 0 093 538 A1

SUSTAINED RELEASE LITHIUM-CONTAINING TABLETS AND METHOD FOR THEIR MANUFACTURE

BACKGROUND OF THE INVENTION

The sustained release lithium carbonate tablets manufactured by the applicant company have been well received by the medical profession.

Lithium salts are employed in the treatment of affective disorders and in particular as a prophylactic in recurrent manic-depressive or depressive illness. The virtue of the sustained release lithium carbonate tablets is that they release lithium at a predetermined rate over a fairly prolonged period, thus enabling the tablets to be taken less frequently than if the lithium was available immediately on consumption of the tablet while still providing an acceptable blood level.

A sustained release lithium carbonate tablet was described in our UK Patent 1 209 093, this tablet comprising -

(i) a powdered therapeutically active lithium salt;

(ii) a sustained release agent comprising a mixture of glyceryl mono-, di- and tri-esters of one or more straight chain C_{16}-C_{18} saturated fatty acids, and

(iii) other innocuous compounding materials.

The tablets may be made by a method which comprises granulation of the above mixture by a moist granulation technique, screening to form a granulate of appropriate grain sizes and compacting the granulate into tablets.

SUMMARY OF THE INVENTION

We have found that difficulties still remained in the manufacture of sustained release lithium carbonate tablets which would give a satisfactory release pattern of lithium over an extended period. In fact, batches of the tablets were found to give release times which exceeded the desired limits - in other words the release of lithium in the usual *in vitro* release pattern testing procedures was too slow and thus, had the tablets been ingested, the release of lithium would have been insufficient to provide a satisfactory therapeutic level.

After considerable investigation and experimentation the cause of the trouble was unexpectedly found to be in the nature of the crystals of lithium carbonate themselves.

According to the present invention we have found that very satisfactory sustained release lithium carbonate tablets can be made, if the lithium carbonate material used in the tablets comprises acicular crystals with an essentially monomodal particle size distribution in which the curve showing volume percentages of particles

of different sizes shows a peak at a particle diameter of between 10 and 25 μm, not more than 20% by volume (preferably less than 10% by volume) of the material having a particle diameter above 30 μm.

A very suitable sustained release agent for coating the lithium carbonate is a mixture of glyceryl mono-, di- and tri-esters of one or more straight chain saturated fatty acids. Such a material is available and sold by Messrs. Gattefosse of France under the Trade Mark "Precirol", the acid radicals being principally the radicals of palmitic and stearic acids.

A method of making the tablets of the present invention comprises the steps of -

(a) mixing (i) acicular crystals of lithium carbonate having an essentially monomodal particle size distribution in which the curve showing volume percentages of particles of different sizes shows a peak at a particle diameter of between 10 and 25 μm, not more than 20% by volume of the material having a particle diameter above 30 μm; (ii) a sustained release agent comprising a mixture of glyceryl mono-, di- and tri-esters of one or more straight chain saturated fatty acids; and (iii) other innocuous compounding materials;

(b) granulation of the said mixture by a moist granulation technique;

(c) screening to form a granulate of appropriate grain sizes; and

(d) compacting the granulate into tablets.

The said other innocuous compounding materials may include a filler such as mannitol, a binding agent such as gum acacia, and a lubricant such as magnesium stearate.

The aforementioned screening should preferably give a granulate whose particles all pass through a sieve with 1.40 mm apertures, where 20 to 30% pass through a sieve with 250 µm apertures while 70 to 80% are retained on a sieve with 250 µm apertures. A lubricant, such as magnesium stearate, may be added to the granulate after screening and before tabletting.

In an embodiment of the invention, not more than 10% of the lithium carbonate material has a particle diameter above 30 µm

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention will be further described with reference to the accompanying drawings, wherein:

Fig. 1 is a scanning electron micrograph of lithium carbonate material previously used and found to give batches of tablets with insufficiently controlled release times;

Fig. 2 is a particle size distribution analysis of the material whose electron micrograph is given in Fig. 1;

Fig. 3 is a scanning electron micrograph of lithium carbonate material found to provide satisfactory tablets; and

Fig. 4 is a particle size distribution analysis of the material whose electron micrograph is given in Fig. 3.

A comparison of Figs. 1 and 3 shows the essential difference between the crystalline lithium carbonate material found to be unsatisfactory, and that found to give reliably constant results. The lithium carbonate of Fig. 1 consists of minute crystals clustered together whilst the material of Fig. 3 has larger, essentially single acicular crystals. Naturally the particle sizes vary, but we have found that satisfactory results are achieved, as long as the curve showing volume percentages of particles of different sizes shows a peak at a particle diameter of between 10 and 25 μm and not more than 20% by volume of the material has a particle diameter above 30 μm. By "particle diameter" we mean the diameter of a circle having the same area as the area of the profile of the particle, as seen by the particle size analyser.

Figs. 2 and 4 show the particle size distribution analyses of the lithium carbonate material shown in Figs. 1 and 3. In each case the analysis is taken on readings given by a HIAC (Trade Mark) Particle Size Analyser (PA-720) using as carrier fluid a 0.5% $^{w}/_{w}$

solution of Span 20 (a non-ionic surfactant, "Span" being a Trade Mark) in toluene. It can be seen that the distribution curve of Fig. 2 shows a number of defined peaks, whilst the particle size distribution of the lithium carbonate material of Fig. 4 is essentially monomodal.

As previously indicated, the lithium carbonate material of Figs. 3 and 4 gives much better results from the point of view of a satisfactory release pattern for therapeutic purposes of lithium than does the material of Figs. 1 and 2. Whilst we do not wish to be bound by any theory as to why this is so, we believe that the coating round the cluster of crystals of the material of Fig. 1 penetrates into the cluster and round, or nearly round individual particles thus to fill or partially fill the void spaces between the individual crystals comprising the cluster, with the result that, when the coating is exposed to the eroding action of fluid and movement in the gastr -intestinal tract, an insufficient proportion of the surface of the lithium carbonate is exposed and available for solution in the body fluids at any given point in time.

Example

A batch was prepared with the following ingredients :

Lithium Carbonate Ph. Eur	60 kg
Precirol	5.85 kg
Mannitol B.P.	9.9 kg

Acacia powder B.P.	3 kg
Sodium Lauryl Sulphate B.P.	318 g
Magnesium Stearate B.P.	375 g
Maize Starch B.P.	3.43 kg

The lithium carbonate was supplied by Metallgesellschaft AG, and was in the form of acicular crystals with not more than 10% having a particle diameter above 30 µm. The particle size distribution was found to be monomodal, the particle size distribution analysis being similar to that shown in Fig. 4.

"Precirol" (Trade Mark) is a mixture of glyceryl mono-, di- and tri-esters of palmitostearic acids, principally palmitic and stearic acids, supplied by Messrs. Gattefosse of France.

The lithium carbonate was blended to ensure uniformity.

The mannitol was sieved through a 600 µm aperture screen and mixed in a mixer with the lithium carbonate and all the other ingredients except the Precirol. The mixer had a jacket for heating by steam or hot water and possessed a horizontal mixer shaft bearing 4 Z-shaped blades. The temperature was measured by means of a metal encased thermometer dipping at least 6 inches into the powder. Mixing and controlled heating were continued until a uniform temperature of 70°C was attained and held for 15 minutes.

An alcoholic solution of Precirol was prepared by dissolving 5.85 kg in 24 litres of alcohol (industrial

methylated spirit), and bringing the temperature of the solution to 72°C. This solution was poured onto the heated powdered mixture of the other ingredients and mixed for 15 minutes. Twelve litres of water were poured onto the mixture and the whole mass was kneaded.

The resulting mass was then dried at 40°C by evaporation, e.g. in an Aeromatic dryer. The crude granulate was then passed through a sieve with 1.40 mm apertures, and submitted to a sieve analysis with necessary adjustment made by adding particles from a previous batch to ensure a correct size distribution, and particularly that between 70 and 80% are retained on a sieve of 250 µm aperture size, while the remainder pass through such a sieve.

The resulting mixture was then compressed into tablets on a rotary tabletting machine with concave tipped rod-shaped punches. The resulting tablets had a weight of about 550 milligrams, a Monsanto hardness of 4 and contained about 400 milligrams of lithium carbonate and 39 milligrams of Precirol.

WHAT IS CLAIMED IS :

1. A sustained release lithium carbonate tablet containing particles of lithium carbonate coated with a sustained release agent characterised in that the lithium carbonate material comprises acicular crystals with an essentially monomodal particle size distribution in which the curve showing volume percentages of particles of different sizes shows a peak at a particle diameter of between 10 and 25 µm, not more than 20% by volume of the material having a particle diameter above 30 µm.

2. A sustained release lithium carbonate tablet according to claim 1 wherein the sustained release agent comprises a mixture of glyceryl mono-, di- and tri-esters of one or more straight chain saturated fatty acids.

3. A sustained release lithium carbonate tablet according to claim 1 or claim 2 wherein not more than 10% of the lithium carbonate material has a particle diameter above 30 µm.

4. A method of making tablets according to claim 1 which comprises the steps of -

(a) mixing (i) acicular crystals of lithium carbonate having an essentially monomodal particle size distribution in which the curve showing volume percentages of particles of different sizes shows a peak at a particle diameter of between 10 and 25 µm, not more than 20% by volume of the material having a particle diameter above 30 µm; (ii) a sustained release agent comprising a mixture of glyceryl mono-, di- and tri-esters of one or more straight chain saturated fatty acids; and (iii) other innocuous compounding materials;

(b) granulation of the said mixture by a moist granulation technique;

(c) screening to form a granulate of appropriate grain sizes; and

(d) compacting the granulate into tablets.

5. A method according to claim 4 wherein the screening is to give a granulate whose particles all pass through a sieve with 1.40 mm apertures, where 20 to 30% pass through a sieve with 250 µm apertures while 70 to 80% are retained on a sieve with 250 µm apertures.

6. A method according to claim 4 or claim 5 wherein not more than 10% of the lithium carbonate material has a particle diameter above 30 µm.

Fig.1

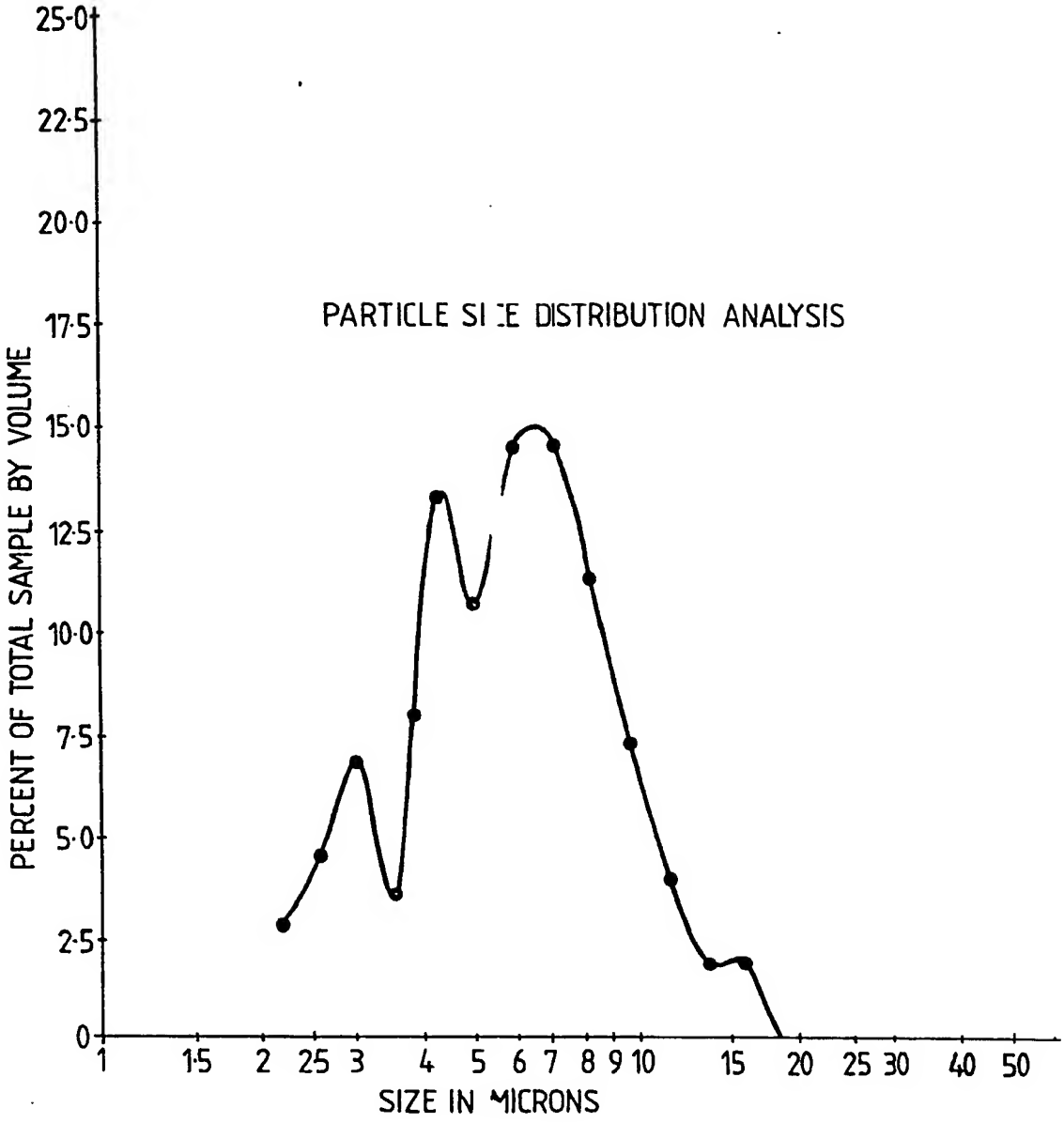
PARTICLE SIZE DISTRIBUTION ANALYSIS
PERCENT OF TOTAL SAMPLE BY VOLUME
25·0
22·5
20·0
17·5
15·0
12·5
10·0
7·5
5·0
2·5
0
1
1·5
2
2·5
3
4
5
6
7
8
9
10
15
20
25
30
40
50
SIZE IN MICRONS

Fig.2

Fig.3

0·1mm

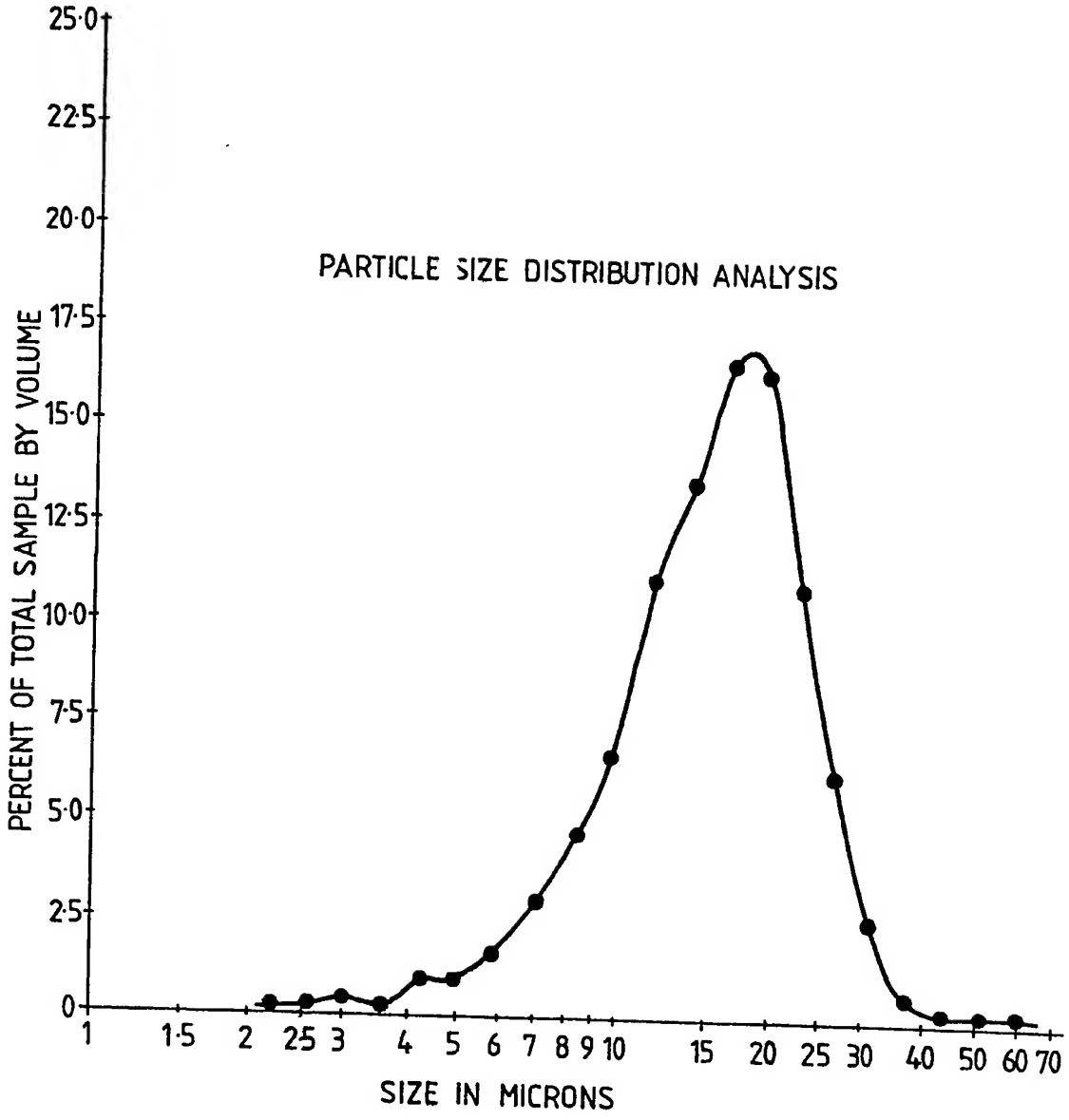
PARTICLE SIZE DISTRIBUTION ANALYSIS
PERCENT OF TOTAL SAMPLE BY VOLUME
25·0
22·5
20·0
17·5
15·0
12·5
10·0
7·5
5·0
2·5
0
1
1·5
2
2·5
3
4
5
6
7
8
9
10
15
20
25
30
40
50
60
70
SIZE IN MICRONS

Fig.4

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 83 30 2216

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	GB-A-2 016 922 (DELANDALE LAB.) * Whole document *	1-6	A 61 K 9/22 A 61 K 33/00
A	GB-A-1 450 536 (DELANDALE LAB.) * Whole document *	1-6	
D,A	GB-A-1 209 093 (DELANDALE LAB.) * Whole document *	1-6	
A	CHEMICAL ABSTRACTS, vol. 90, no. 6, 5th February 1979, pages 304-305, no. 43735u, Columbus, Ohio, USA K. VENTOURAS et al.: "Role of technological factors on the release from hydrophilic matrixes" & EXPO. - CONGR. INT. TECHNOL. PHARM., 1st 1977, 4, 104-113 * Whole abstract *		

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

A 61 K 9/00
A 61 K 33/00
C 01 D 15/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	13-07-1983	BENZ K.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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